

Oral Pioglitazone Reduces Infarction Volume and Improves Neurologic Function At Doses Used In Clinical Practice.

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Thiazolidinediones (TZDs), including pioglitazone, are protective in rodent stroke models using intra-peritoneal, intra-venous and inter-ventricular routes of administration. Pioglitazone is an attractive neuroprotective agent because it is used clinically to treat type 2 diabetes. Large numbers of patients, at high risk for stroke, take pioglitazone daily. If pretreatment with oral pioglitazone were neuroprotective, this would be extremely clinically relevant, provided that doses were similar to those used to treat diabetes. One study previously tested pretreatment with oral pioglitazone in rats, but the dose was 30 times that used in humans, although TZD metabolism is similar in both species. We tested the hypothesis that pretreatment with oral pioglitazone reduces infarction volume following MCAO in the rat suture model. Pioglitazone was dissolved in DMSO in order to accurately measure the small volumes required. Wistar rats were given 10 microliters of DMSO or pioglitazone dissolved in DMSO (0.65 mg/Kg_45 mg in a 70 Kg man, 0.40 mg/Kg_30 mg in a 70 Kg man, or 0.20 mg/Kg_15 mg in a 70 Kg man) daily for five days prior to 2 hour MCAO. Temperature, blood pressure and arterial blood gases were monitored and kept within normal range. Cerebral blood flow (CBF) was monitored and only animals with at least a 60% drop in CBF which was sustained at the time of reperfusion were included. We have previously shown that TZDs do not alter blood pressure, CBF or serum glucose in non-diabetic rats. Animals underwent serial functional analysis using the modified neurologic stroke scale (mNSS) which tests both motor and sensory function as well as the adhesive sticker test, which tests the rats ability to sense and remove an adhesive sticker from the forepaw. Twenty one days after MCAO rats were sacrificed and infarct volumes determined. We find significant reductions in the volume of infarction with all doses tested. While the brains from animals treated with vehicle alone displayed infarction throughout the MCA distribution (47.33% of the volume of the contralateral hemisphere, sem_0.83, n_4), the 0.65 mg/kg dose reduced infarction volume to 25.09% (p_0.01, sem_5.45, n_8). The 0.40 mg/kg dose reduced infarction volume to 22.85% (p_0.05, sem_6.82, n_5) and the 0.20 mg/kg dose reduced infarction volume to 40.05% (p_0.05, sem_1.4, n_3). Over time the animals treated with either 0.65 mg/kg or 0.40 mg/kg pioglitazone had improved performance on both the mNSS and the adhesive sticker test (p_0.05; one way ANOVA). Although, the 0.20 mg/kg dose significantly reduced infarction volume the magnitude of the reduction was modest and did not translate into improved neurologic function. These data indicate that oral pioglitazone is effective at reducing injury and improving neurologic outcome at doses similar to those used to treat diabetes.